

Leukocyte Reduction in Non-Targeted Populations

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Background

- CMV transmission [1]
 - RCT: HPC transplant
 - CMV seronegative vs. bedside leukocyte reduced
 - Outcome measure: CMV infection in 100 days
 - Equivalent rate of CMV infection: 1.3% v 2.4%
 - Higher rate of CMV disease: 0% v. 2.4%

Background

- HLA alloimmunization [3]
 - RCT: AML
 - RDPC v. F-RDPC v. UVB-RDPC v. F-SDP
 - Outcome measure: alloimmunization, platelet refractoriness
 - LCT: 45% v. 18% v. 21% v. 17%
 - Refractory: 16% v. 7% v. 10% v. 8%
 - SDP no additional benefit

Background

- Febrile non-hemolytic transfusion reactions
 - Multiple observational studies
 - Prospective case controlled studies using various leukocyte reduction methods

“Targeted” Populations

- HPC transplantation
- Acute or chronic leukemia
- Lymphoma
- Solid organ transplantation
- Congenital immune deficiency
- Acquired cellular immune deficiency
- Intrauterine transfusion
- Chronic transfusion requirement

Objectives of This Review

- Review clinical studies published in the last 4 years of the impact of leukocyte reduction of cellular blood components
 - CMV transmission
 - Alloimmunization
 - Febrile transfusion reactions
 - Clinical outcomes

Data Sources

- Study types
 - Randomized clinical trials
 - Cohort “before and after” studies
 - Meta-analyses
- References at end of presentation

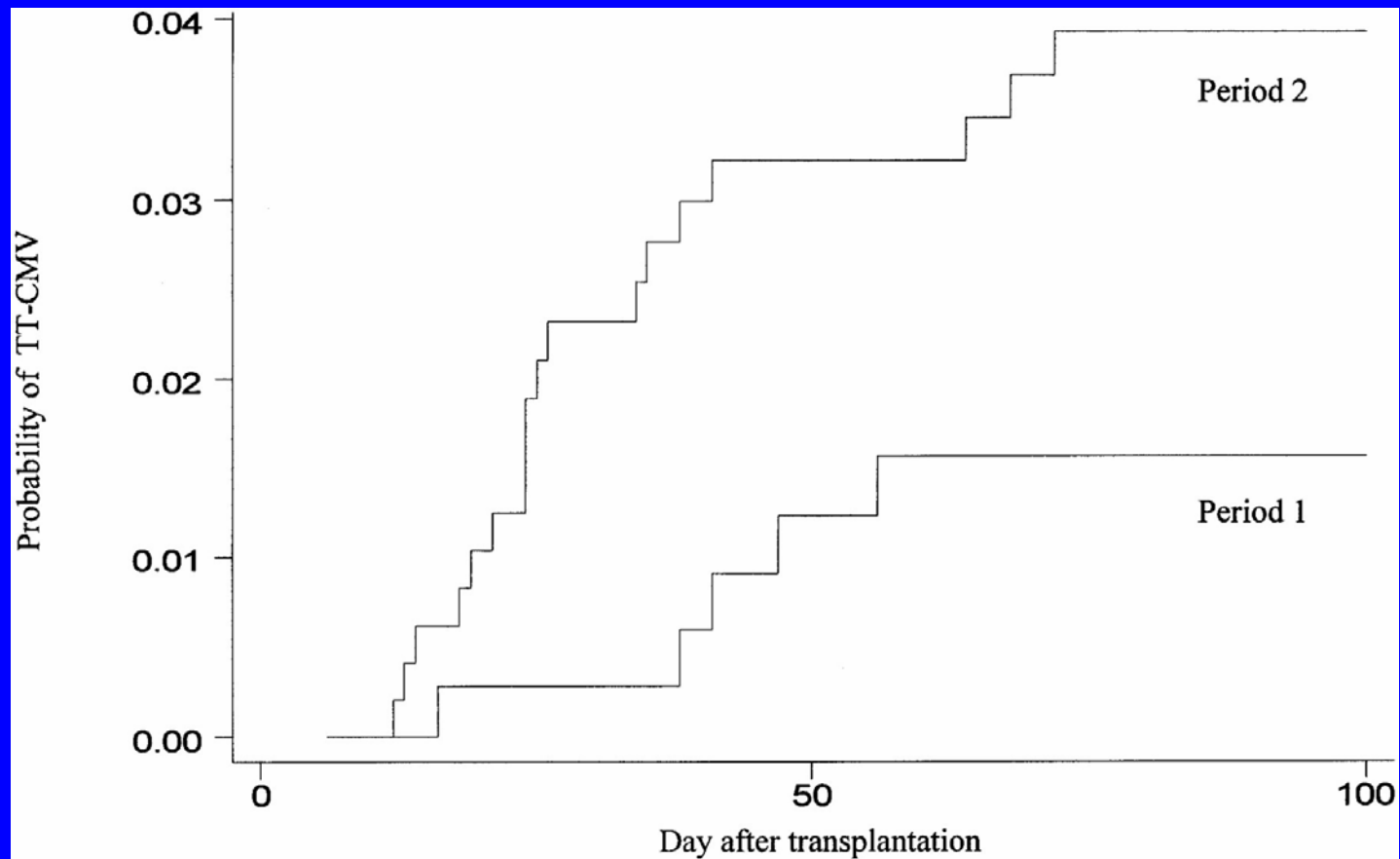
CMV Transmission

- Prospective cohort study: HPC transplant [2]
- CMV seronegative donor/recipient pairs
- Period 1: 5/94 - 11/96
 - RDPC + SDP: post-storage filtration
 - RBC: pre-storage filtration
- Period 2: 12/96 - 2/00
 - SDP: LR by centrifugation
- Outcome measures: CMV antigenemia by day 100

Blood Components

- LR failures
 - RBC: 0.2% (mean 6.0×10^6)
 - RDPC: 0%
 - SDP: 0.4% (mean 15.1×10^6)
- CMV+ donors
 - RBC: 1.2%
 - RDPC: 1.6%
 - SCP: 8.0%

Incidence of CMV Antigenemia



Blood Component Support

	CMV n=24	No CMV n=783
Total units	55 \pm 8	36 \pm 2
Total CMV- units	47 \pm 7	34 \pm 2
Total CMV+ units	7 \pm 2	3 \pm 0.3
CMV+ RBC	0.9 \pm 0.6	0.1 \pm 0.1
CMV+ RDPC	0.3 \pm 0.2	0.3 \pm 0.1
CMV+ SDP	6 \pm 2	2 \pm 0.2

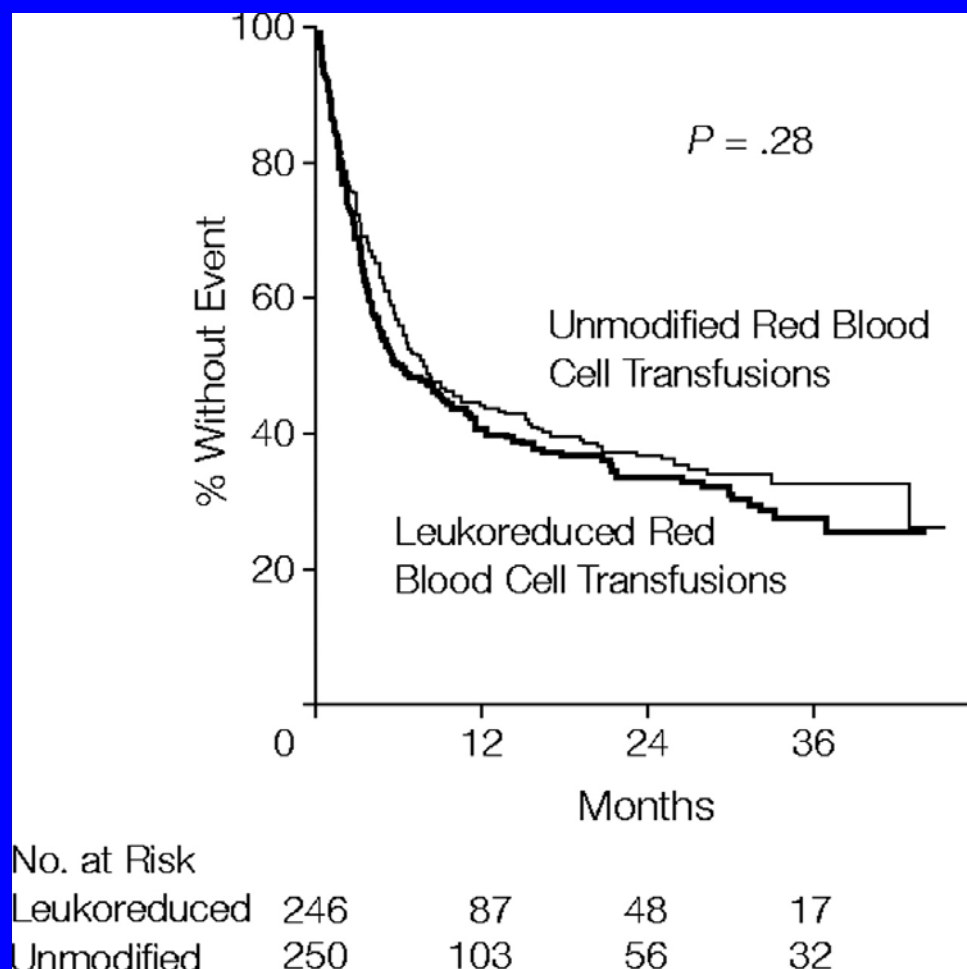
Outcomes

- CMV antigenemia
 - 24/807 (3.0%) patients
 - 21 received preemptive ganciclovir
- No CMV disease

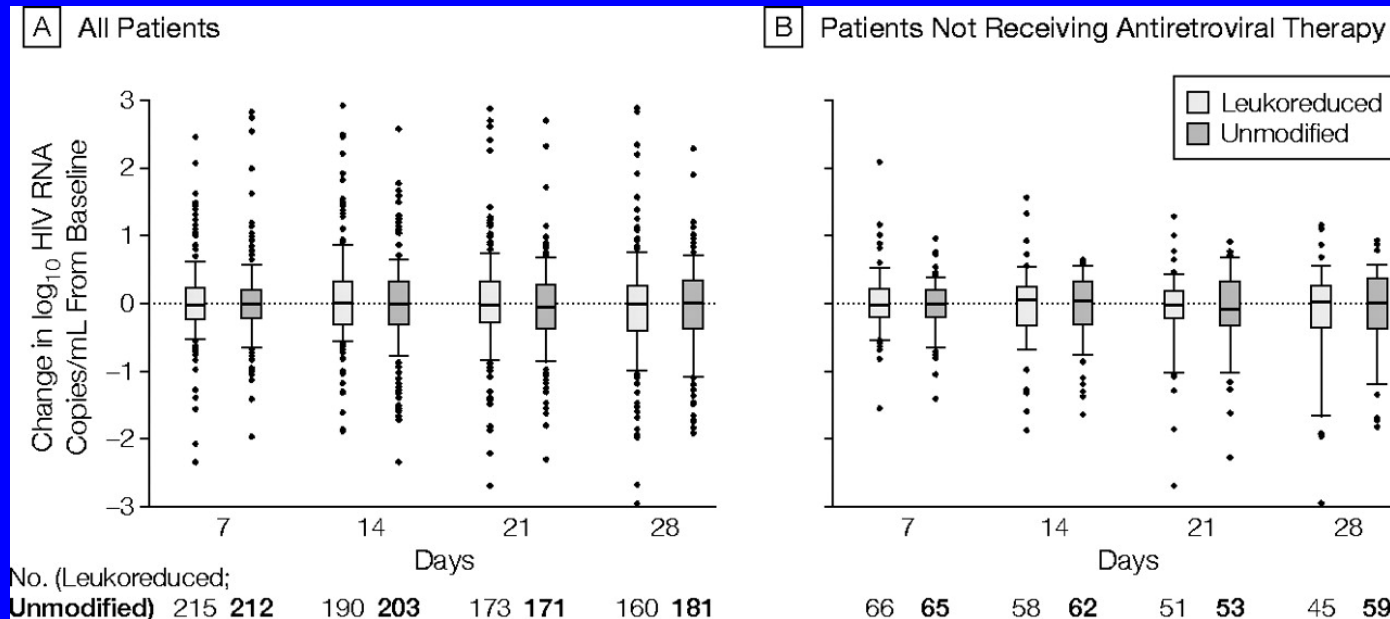
Viral Activation in HIV

- Double blind RCT: HIV and CMV infection [15]
- Unmodified RBC v. LR-RBC
- Outcome measures: HIV RNA, CMV DNA, survival
- 531 patients received 3864 units
- No difference in baseline characteristics or transfusion treatment

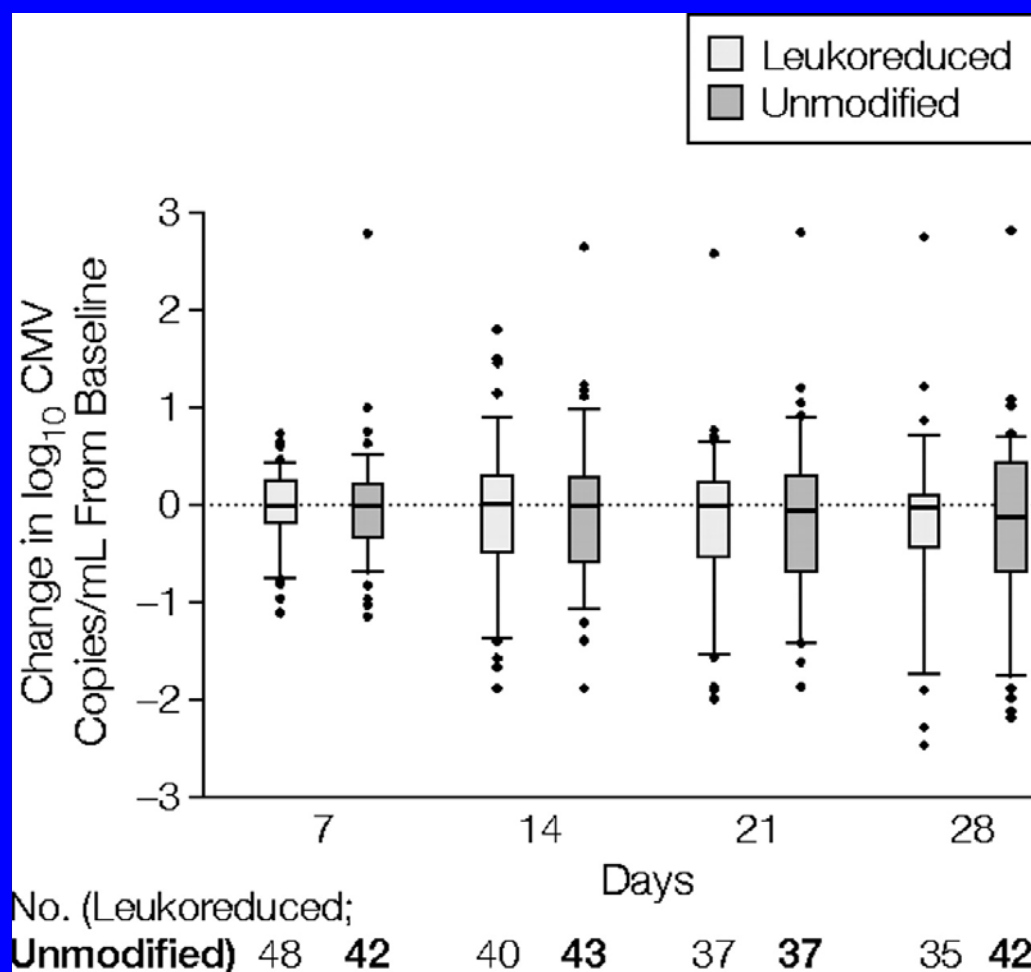
Time to First Serious HIV-Related Complication or Death



Plasma HIV RNA Following Transfusion



CMV DNA Titer Following Transfusion



Alloimmunization

- Retrospective cohort study: acute leukemia and HPC transplant [14]
- Period 1: 1/94 - 11/97
 - <10% LR
- Period 2: 8/99 - 7/02
 - 100% LR
- Platelet transfusion threshold reduced 5/98
- Outcome measure: LCT antibody and platelet refractoriness

Platelet Transfusions

	Pre-ULR	Post-ULR
Transfusions/pt	28 \pm 31	17 \pm 20
Donor exposures/pt	107 \pm 119	61 \pm 69
HLA matched SDP	7%	3%
Pts. receiving HLA matched	16%	5%

Alloimmunization

	Pre-ULR	Post-ULR
Overall	19%	7%
Nulliparous/ nontransfused	25%	11%
Parous only	15%	10%
Transfused only	29%	2%

Platelet Refractoriness

	Pre-ULR	Post-ULR
Overall	40%	23%
Alloimmune refractory	14%	4%
Nulliparous/ nontransfused	8%	2%
Parous only	11%	9%
Transfused only	20%	0%

Alloimmunization

- RCT: Cardiac surgery [11]
- Buffy-coat depleted RBCs v. Prestorage filtered RBCs v. Post-storage filtered RBCs
- Outcome measures: LCT antibodies at 3-10 weeks and 20-30 weeks

Patient Characteristics

	Control	Pre-LR	Post-LR
Prior transfusion or pregnancy	41.5%	36.8%	48.2%
RBCs transfused	4 (2;6)	4 (2;6)	4 (3;6)
Platelet transfusions	7.0%	6.4%	8.8%

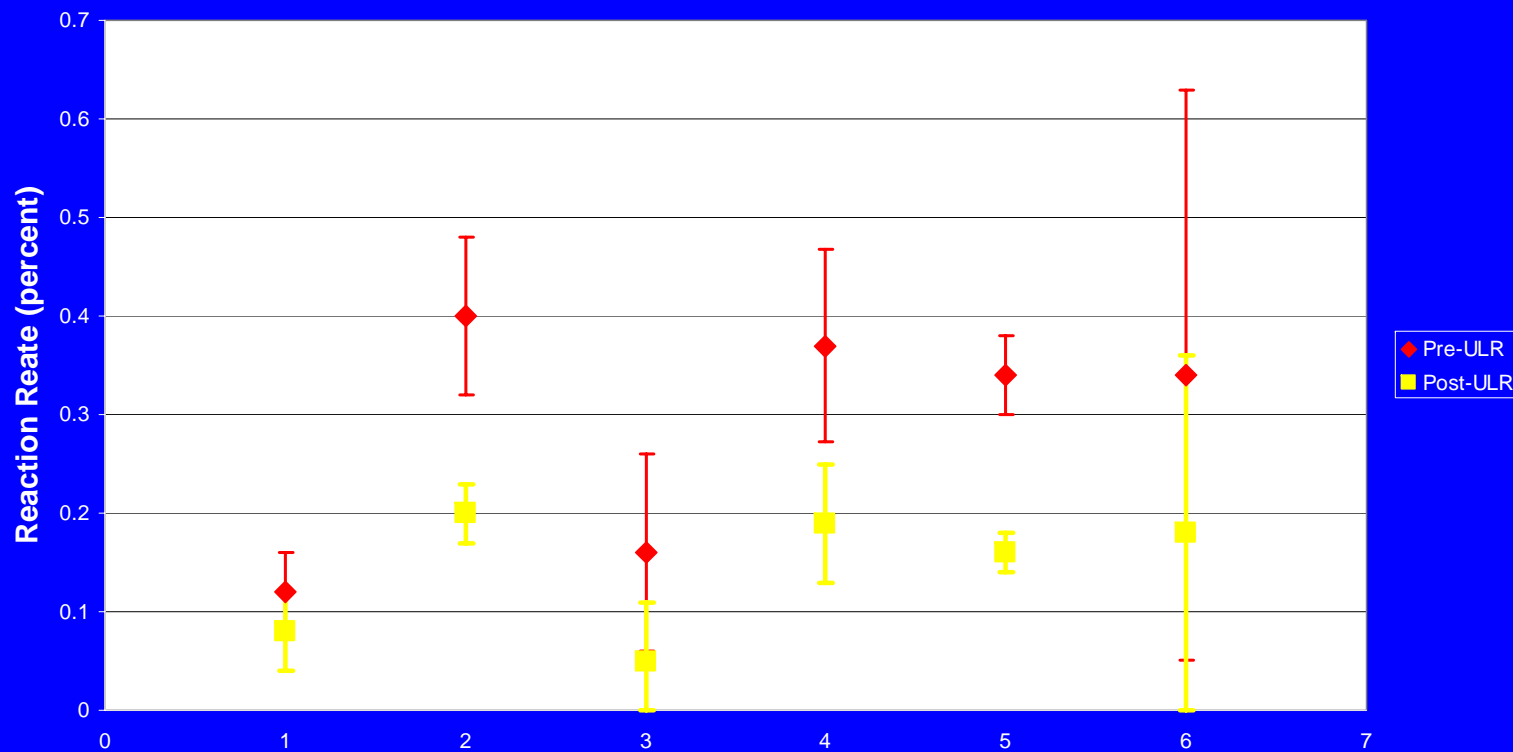
LCT Antibody Responses

Pre	Post	Control	Pre-LR	Post-LR
-	-	66.2%	68.0%	71.5%
-	+	9.9%	11.3%	7.2%
+	++	6.2%	7.0%	7.2%
+	-	8.7%	8.5%	8.8%
+	+	6.7%	7.0%	8.8%

Febrile Transfusion Reactions

- 6 retrospective cohort studies, 1 RCT [4,5,6,7,8,9]
- FNHTR: Diagnosis of exclusion
- Data reported as reactions/total units transfused
- Confidence intervals calculated from published data

Febrile Transfusion Reaction Rates



Trap Study

- Analysis of transfusion reactions [23]
- Febrile and chill/rigor rxns extracted
- Control
 - 2.5% (1.8;3.2)
- Filtered RDPC
 - 1.6% (1.1;2.1)
- Rxns associated with $>5 \times 10^6$ WBC and storage > 2 days

Outcome Studies

- RCT: general hospital population [6]
- Patients with specific LR indications excluded
- Unmodified RBC and RDP v. Prestorage LR RBC and process LR SDP
- Outcome measures: in-hospital mortality, post-transfusion length of stay

Major Patient Characteristics

	Control n=1425	LR n=1355
Nonsurgical	38.0%	39.5%
Surgical	62.0%	60.5%
Cardiothoracic	20.9%	20.4%
Orthopedic	15.0%	15.8%
Pulmonary	8.4%	7.2%
Vascular surgery	8.9%	7.0%
Cardiology	7.4%	8.0%

Primary Outcomes

	Control	LR
Mortality	8.5%	9.0%
Length of Stay	6.4 (1.7,23.2)	6.3 (1.7,22.3)

Subgroup Analysis

	Mortality		Median LOS	
	Control	LR	Control	LR
Cardiac surgery	5.4%	6.9%	6.7	6.7
Colorectal surgery	7.3%	9.1%	9.7	9.8
Other surgery	7.7%	8.3%	7.0	7.1
Nonsurgical	10.9%	10.7%	5.2	4.7

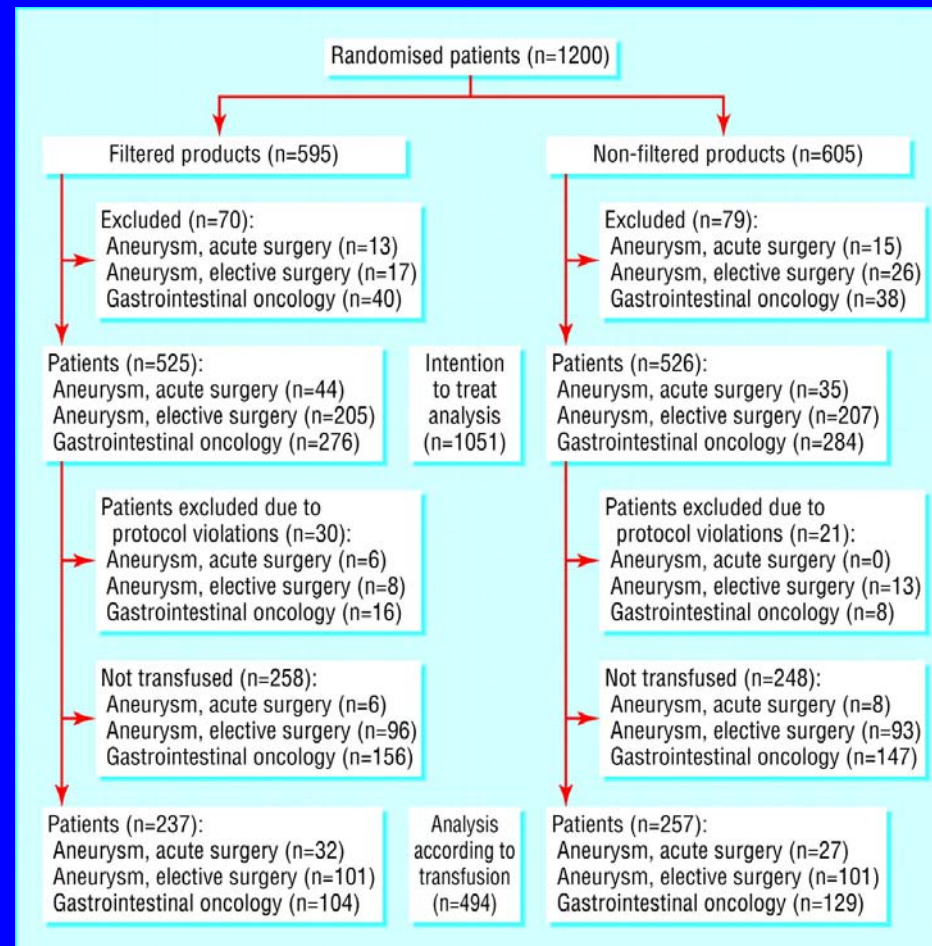
Concerns Raised About This Study

- Age of RBC units
 - Control: 11.5 ± 7.6 days, LR: 18.3 ± 8.8 days
- Source of platelets
 - Control: pools of 6 RDPC, LR: process LR SDP
- Exclusion of patients with LR indications
- Protocol violations
 - Control: 9.3%, LR: 12.6%

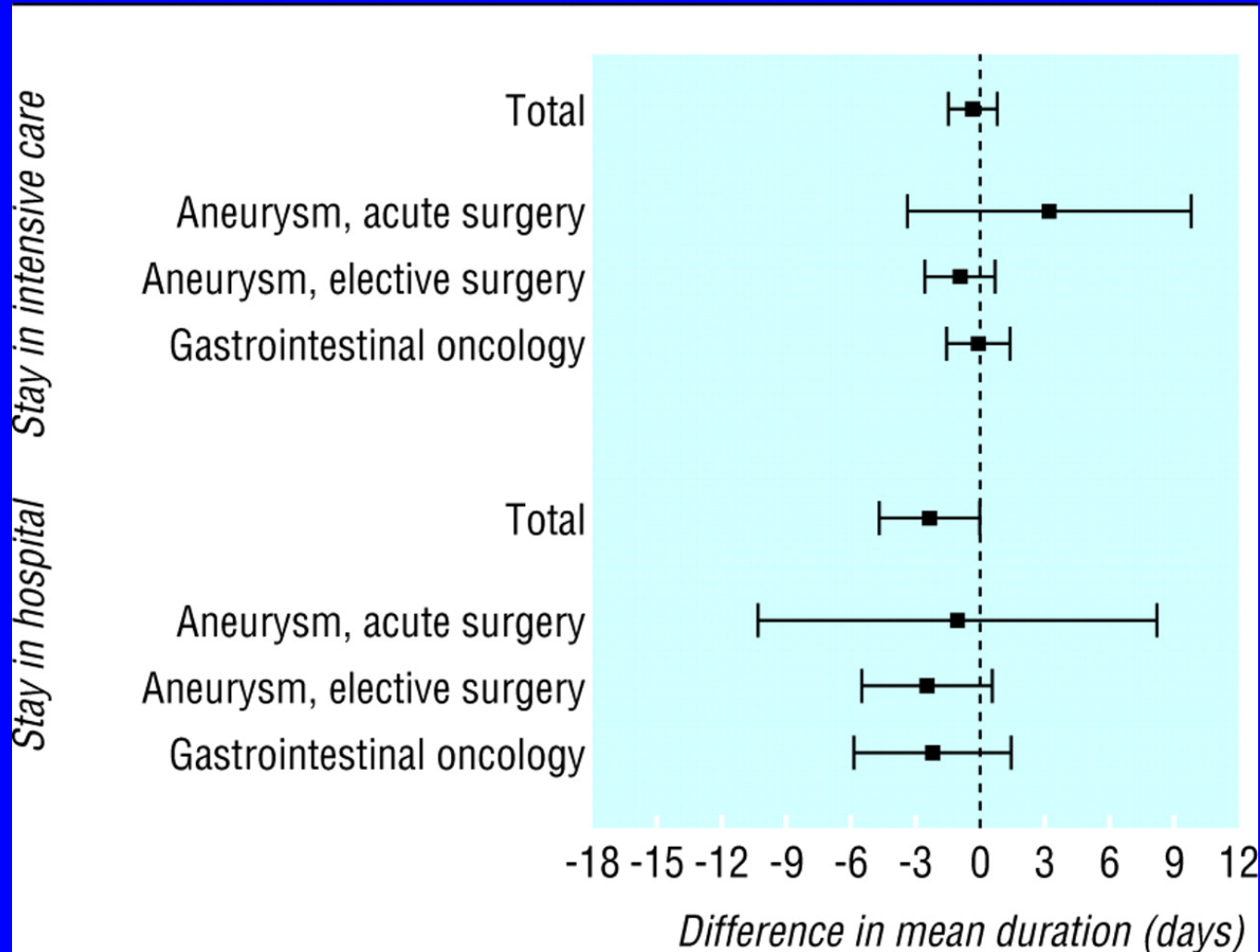
Leukoreduction of RBC in Major Surgery

- RCT: aortic aneurysmectomy and gastrointestinal surgery [18]
- Buffy coat depleted RBCs v. filter LR RBCs
- Outcome measures:
 - Mortality, ICU stay
 - Multi-organ failure, infection, hospital LOS

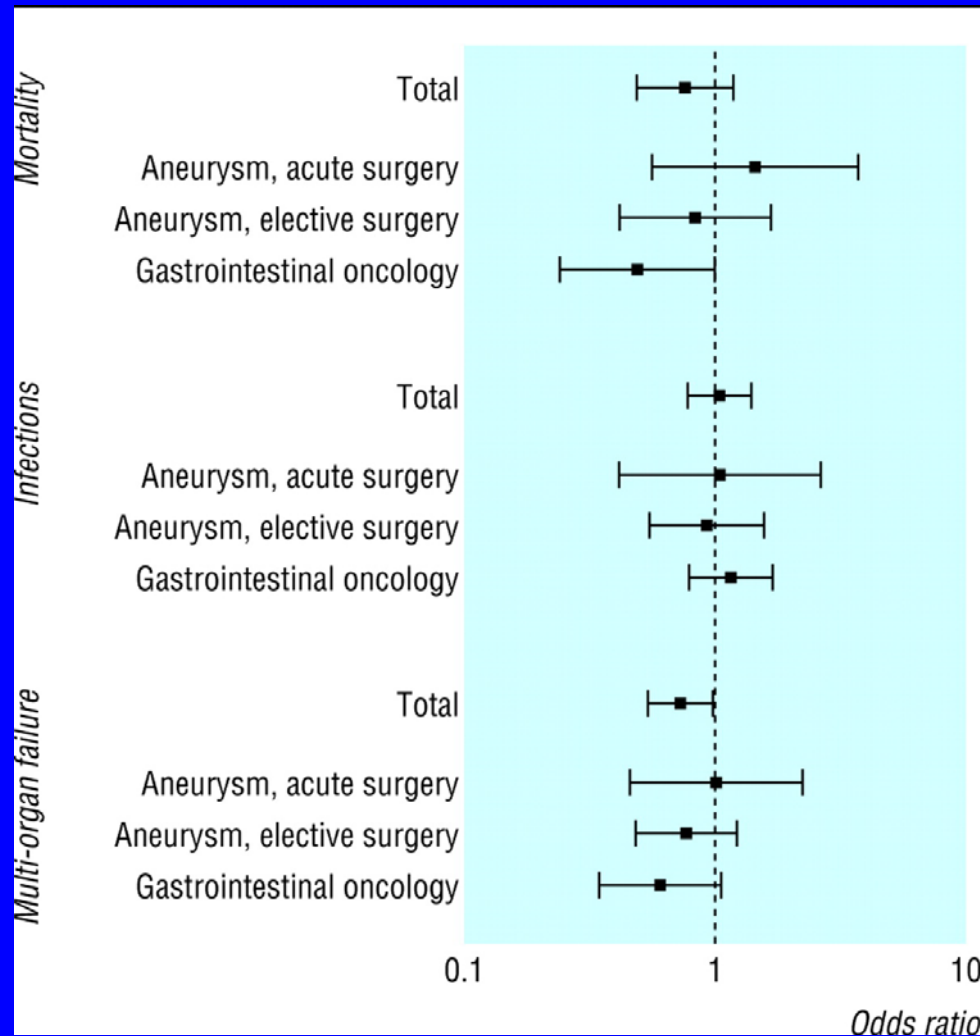
Trial Profile



Intention-to-Treat Analysis



Intention-to-Treat Analysis



Subgroup Analysis

- 494 transfused subjects (47%)
- Mortality
 - Overall: OR 0.74 (0.44;1.24)
 - GI surgery: OR 0.53 (0.17;1.25)
- Multi-organ failure
 - Overall: OR 0.74 (0.49;1.16)
- LOS
 - Overall 4.5 days less (p=0.032)

Infection Rates in Cardiac Surgery

- RCT: CABG, AVR, MVR [10]
- Plasma-depleted RBCs v. Buffy coat-depleted RBCs v. Filtered LR RBCs
- Outcome measures
 - Hospital-acquired infection
 - Length of stay, fever

In-Hospital Infections

	Filtered	BCD	PR
All patients p=0.1	11.3%	10.8%	17.7%
Transfused patients p=0.02	12.6%	11.0%	20.2%

Postoperative Outcomes

	Filtered	BCD	PR
LOS	7 (3-42)	6 (3-27)	7 (3-55)
Patients with fever p=0.02	30.8%	32.4%	43.3%
Days of fever	95	120	136
Days at risk	1124	1170	1129

Leukocyte Reduction of RBC in Cardiac Surgery

- Double blind RCT: valve replacement \pm CABG [17]
- Buffy coat-depleted RBCs v. Filtered LR RBCs
- Outcome measures:
 - 90-day mortality
 - In-hospital mortality, LOS, infections

Intention-to-Treat Analysis

	BCD	LR	Odds Ratio
90-day mortality	12.7%	8.4%	1.52 (0.84-2.73)
In-hospital mortality	10.1%	5.5%	1.99 (0.99-4.00)
Infection	31.6%	22.6%	1.64 (1.08-2.49)
MODS	20.7%	20.4%	10.7 (0.67-2.49)

Analysis of Transfused Patients

	OR	95% CI
90-day mortality	1.52	0.84 – 2.73
In-hospital mortality	1.99	0.99 – 4.00
>3 units	2.43	1.16 – 5.12
Infections	1.64	1.08 – 2.49

Leukoreduction of RBCs in Elective Aortic Surgery

- Retrospective cohort study: abdominal aortic surgery [13]
- Pre-ULR: 1/95-3/98 v. Post-ULR: 4/98-10/00
- Unmodified or buffy coat-depleted RBCs (192 pts) v. Filtered LR RBCs (195 pts)
- Outcome measures: 30-day mortality, infections

Differences in Study Groups

	Control	LR
Hypertension	50.5%	68.7%
Diuretics	12.5%	21.5%
CAD	30.7%	19.0%
Prior PTCA or CABG	15.6%	9.2%
Respiratory insufficiency	9.2%	4.2%

Major Outcomes

	Control (95% CI)	LR (95% CI)
Death	8.9% (4.8%-12.9%)	5.6% (2.4%-8.9%)
Infections	31.3% (24.7%-37.8%)	26.7% (20.5%-32.9%)

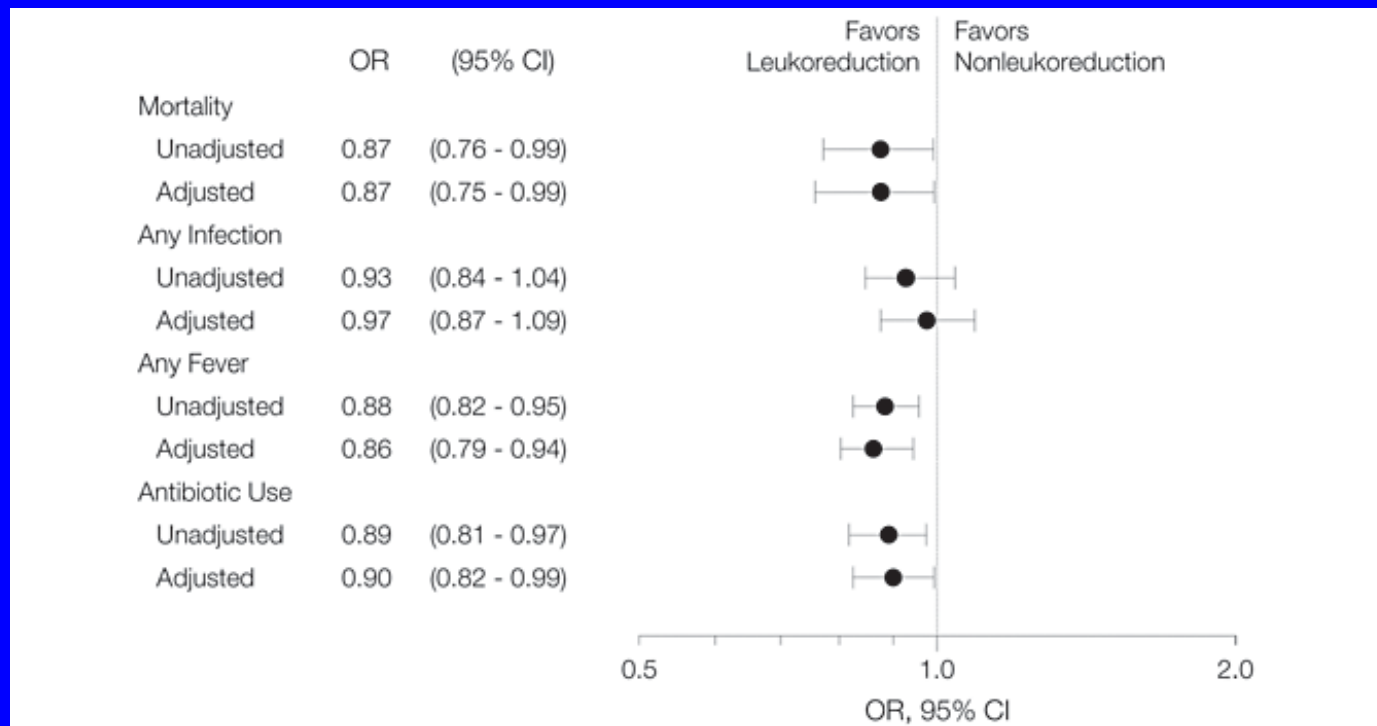
ULR in Canada

- Retrospective cohort study: RBC transfusion for cardiac surgery, hip repair, surgical ICU admission, trauma [24]
- 1-year prior to ULR v. 1-year post
- Unmodified RBCs v. Filtered LR RBCs
- Outcome measures: In-hospital mortality, serious noscomial infections (pneumonia, bacteriemia, sepsis, wound infection)

Differences in Study Populations

	Pre-ULR	Post-URL	Difference (95% CI)
Severe lung disease	5.3%	4.2%	1.1% (0.41;1.79)
β -blockers	45.1%	49.0%	-3.89% (-5.50; -2.28)
Aspirin	45.2%	47.2%	-2.08% (-3.69;-1.47)
ACE inhibitors	30.7%	35.8%	-5.09% (-6.61;-3.57)
Transfusion rate	50.7%	48.8%	-1.95% (-2.80;-1.09)

Odds of Mortality or Infection



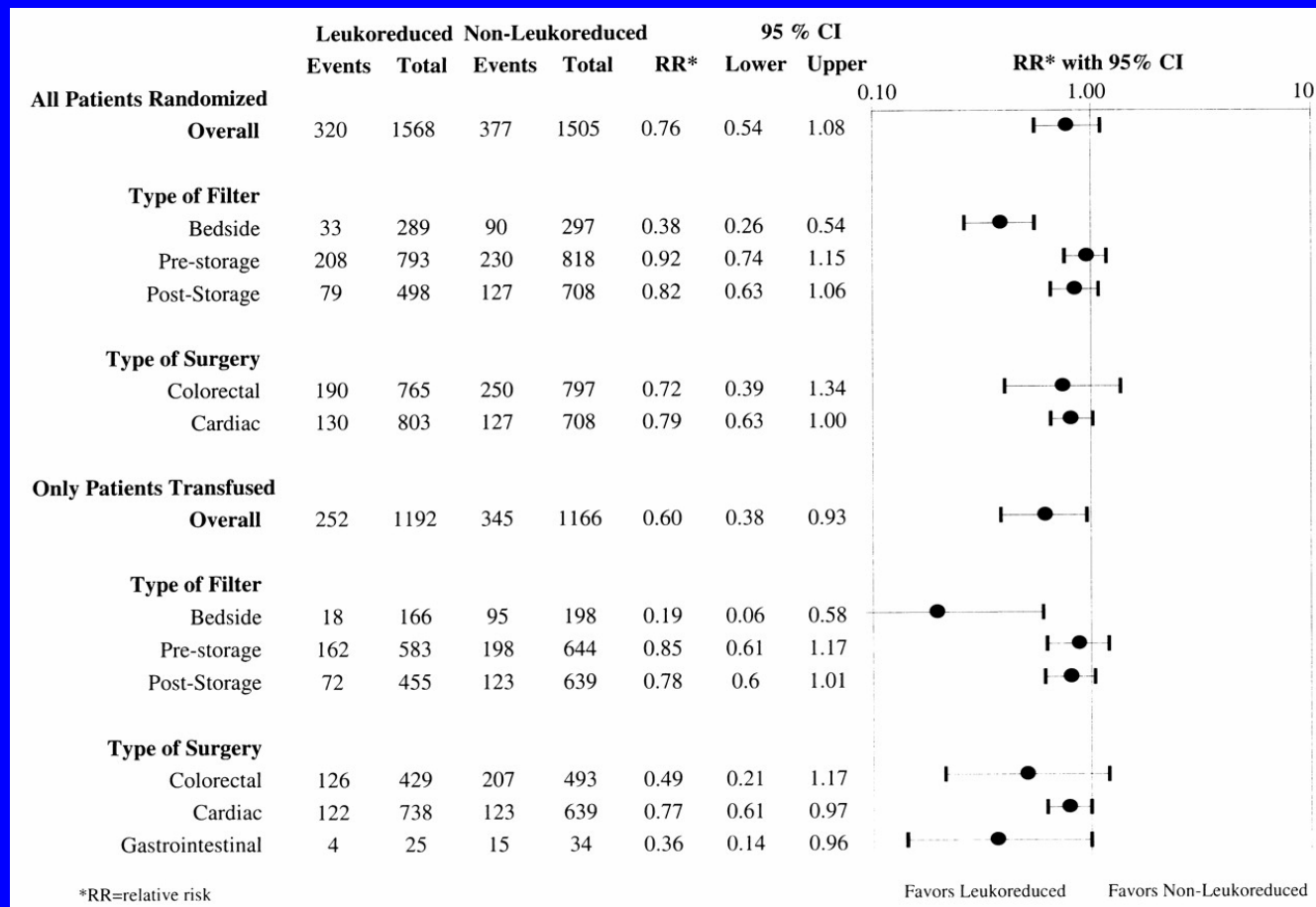
Medication Confounders

- The use of cardiac medications including aspirin, β -blockers, and angiotensin-converting enzyme inhibitors all resulted in the unadjusted OR for mortality shifting from a significant to a nonsignificant association.

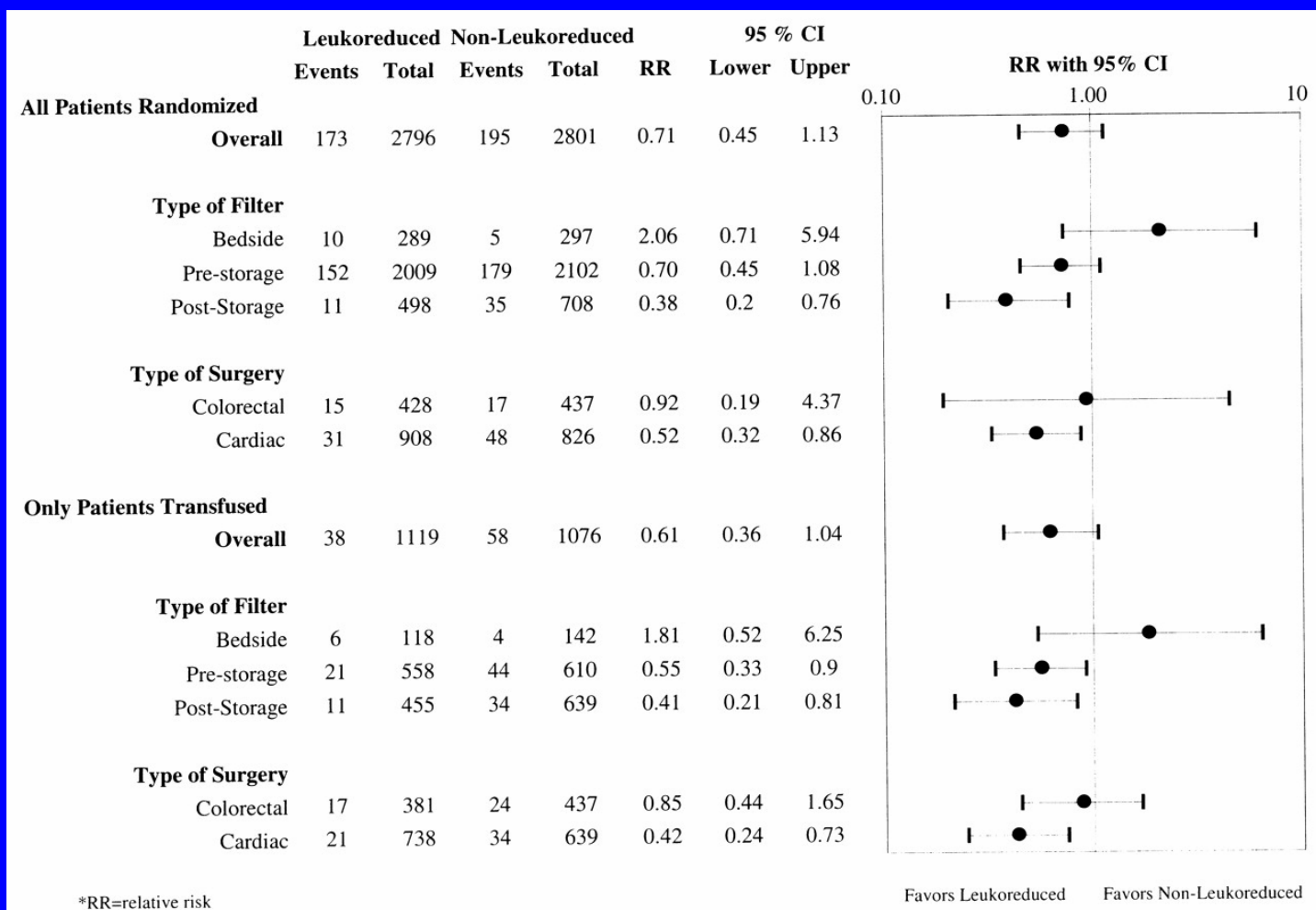
Meta-analysis of RCTs

- RCTs comparing LR allogeneic to non-LR allogeneic RBC transfusions. [19]
- 10 surgical studies included
 - 3 cardiac, 4 colorectal, 1 GI, 2 mixed
 - Proportion not transfused 2% - 73%
 - 1 study blinded physicians
 - 6 pre-storage, 4 post-storage, 2 bedside LR
- Intention-to-treat and subgroup analysis

Postoperative Infections



Mortality



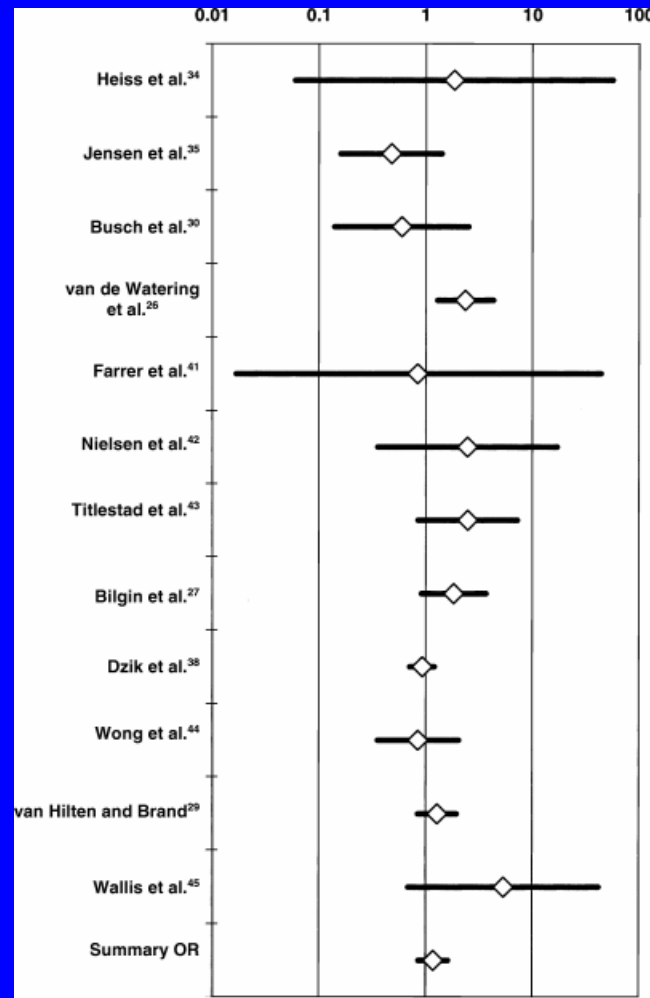
Intention-to-Treat v. Subgroup Analysis

- Randomized population is analyzed in intention-to-treat
- Positive effects seen in intention-to-treat are robust
- Untransfused subjects dilute the power of a study
- Subgroups may not be representative of the randomized population
- Unblinded studies are particularly susceptible to bias in subgroups

Meta-analysis of RCTs

- RCTs comparing LR allogeneic and/or autologous RBC or WB to allogeneic RBC or WB transfusion [20]
- 12 studies included
 - 3 cardiac surgery, 4 colorectal surgery, 2 aortic surgery, 1 mixed surgery, 1 burn trauma, 1 mixed hospital pts.
 - 4 autologous blood
- Intention-to-treat analysis only

Short-Term Mortality



Favors control Favors LR

Colorectal CA

Colorectal CA

Colorectal CA

Cardiac

AAA

Burn surgery

Colorectal CA

Cardiac

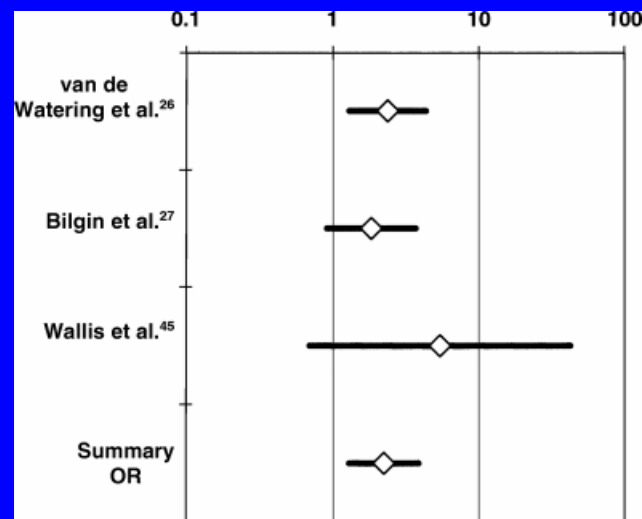
General hospital

AAA

Mixed surgery

Cardiac

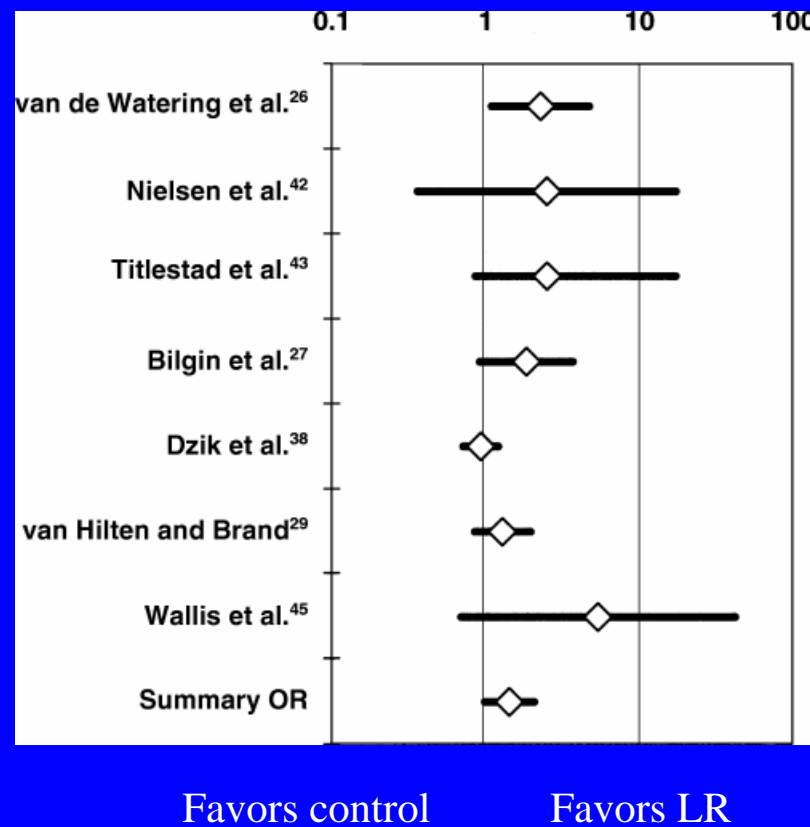
Cardiac Surgery



Favors control

Favors LR

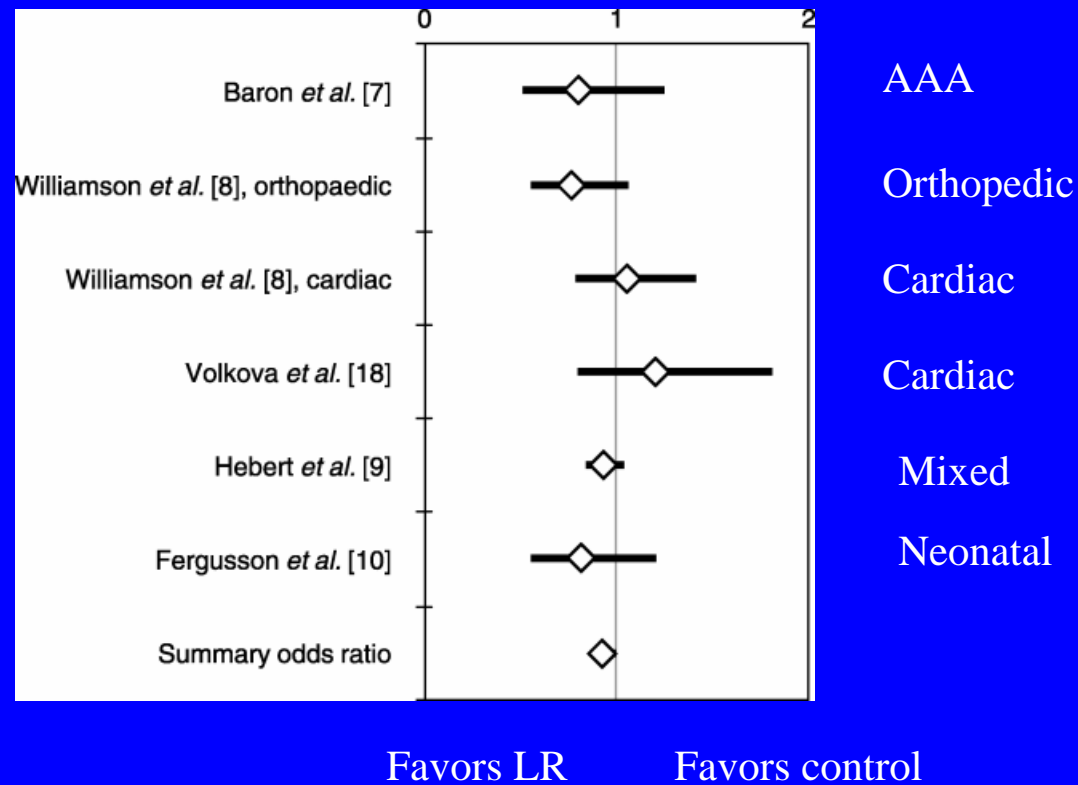
Pre-Storage Leukocyte Reduction



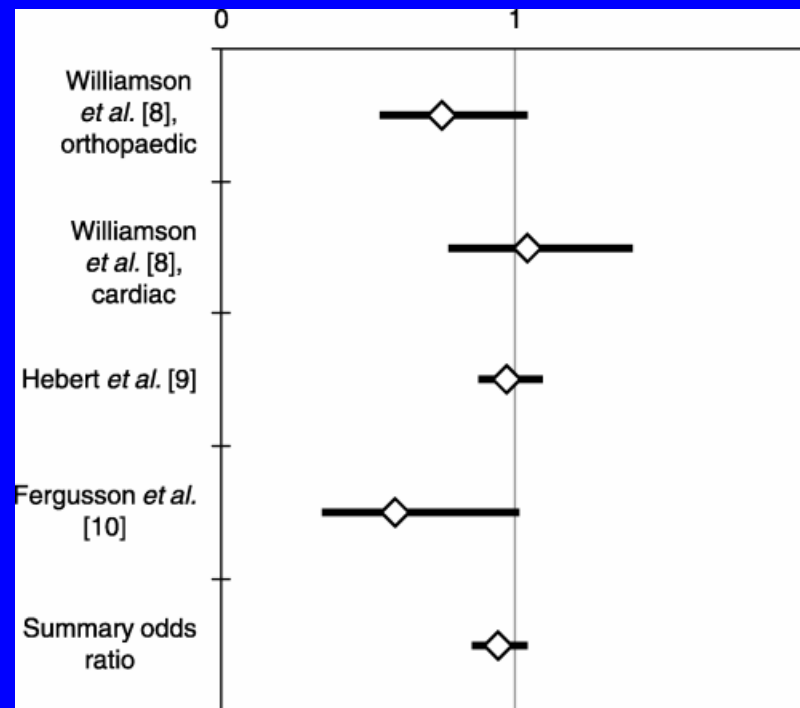
Meta-analysis of “Before and After” Studies

- Cohort studies reporting postoperative infection and/or mortality before and after implementation of ULR [16]
- 6 studies included
 - 2 cardiac surgery, 1 aortic surgery, 1 orthopedic/cardiac surgery, 1 mixed surgical, 1 neonatal

Unadjusted Postoperative Infection



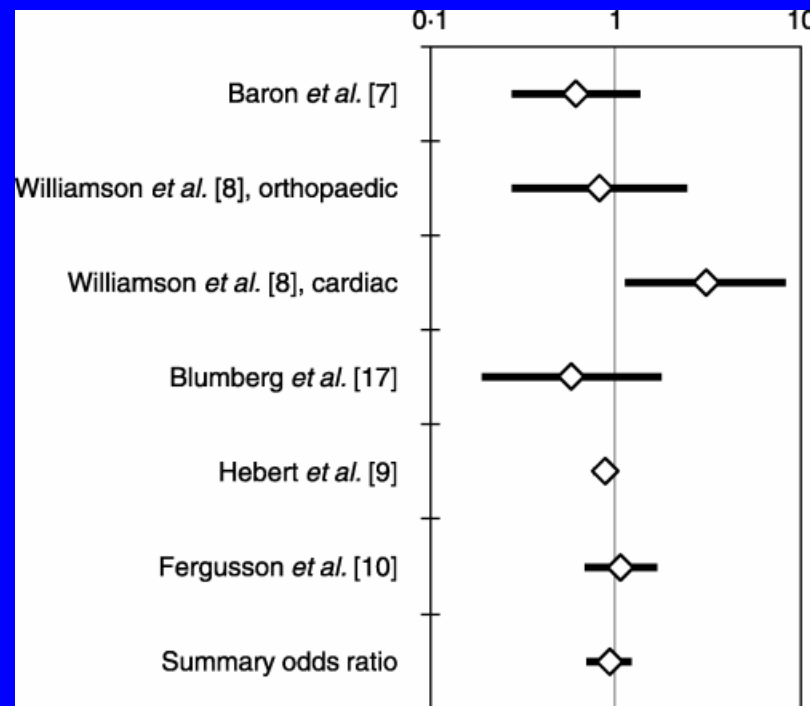
Adjusted Postoperative Infection



Favors LR

Favors control

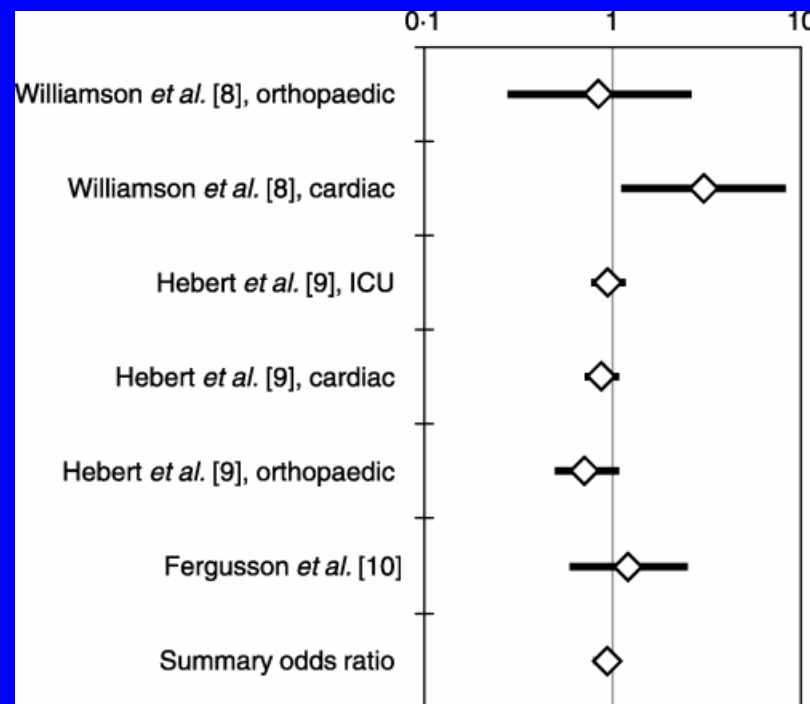
Unadjusted Mortality



Favors LR

Favors control

Adjusted Mortality



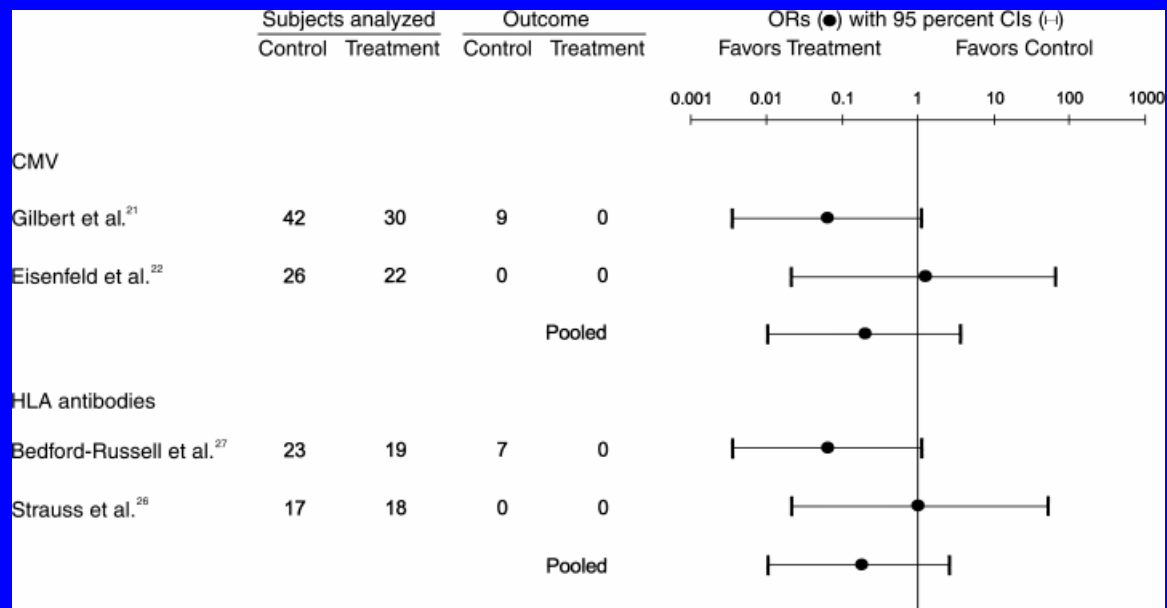
Favors LR

Favors control

Neonatal Transfusion

- Systematic review of clinical trials of LR in neonatal transfusion [25]
- 2 RCTs, 1 before and after study, 1 non-randomized controlled trial identified
- Outcome measures
 - CMV transmission - 2 studies
 - HLA immunization - 2 studies

Pooled Analysis



Conclusions

- CMV transmission by LR components is low.
- LR does not effect the course of HIV infection.
- HLA alloimmunization and platelet refractoriness are reduced by LR but the effect may not be apparent in single transfusion episodes or previously exposed individuals.

Conclusions

- LR reduces but does not eliminate febrile transfusion reactions. Interpretation of reports is difficult due to the subjective nature of the diagnosis.
- Short-term mortality in cardiac surgery appears to be modestly reduced by LR.

Conclusions

- LR appears not to have a significant effect on post-operative infections. Interpretation of studies is difficult because of varying definitions of infection.
- A beneficial effect of LR in general hospital populations has not been demonstrated.

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